(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 617 963 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
21.08.1996 Bulletin 1996/34

(51) Int. Cl.[6]: **A61K 31/665**

(21) Application number: **94104839.9**

(22) Date of filing: **27.03.1994**

(54) Lipid metabolism improving medicinal composition

Zusammensetzung zur Förderung des Lipidmetabolismus

Composition pour améliorer le métabolisme lipidique

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **31.03.1993 JP 73814/93**

(43) Date of publication of application:
05.10.1994 Bulletin 1994/40

(73) Proprietor: **Senju Pharmaceutical Co., Ltd.**
Osaka-shi, Osaka 541 (JP)

(72) Inventors:
- **Ogata, Kazumi**
  Toyonaka-shi, Osaka 565 (JP)
- **Sakaue, Takahiro**
  Itami-shi, Hyogo 664 (JP)
- **Umegaki, Yasuko**
  Kobe-shi, Hyogo 651-21 (JP)
- **Nagao, Rie**
  Neyagawa-shi, Osaka 572 (JP)

(74) Representative: **von Kreisler, Alek, Dipl.-Chem. et al**
Patentanwälte,
von Kreisler-Selting-Werner,
Bahnhofsvorplatz 1 (Deichmannhaus)
50667 Köln (DE)

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- **ARZNEIMITTELFORSCHUNG vol. 42, no. 9 , 1992 pages 1072 - 1074 Y. KURIBAYASHI ET AL 'In vitro studies on the influence of L-ascorbic acid 2-[3,4-di hydro-2,5-tetramethyl-2-(4,8,12-trimethylt ridecyl)-2H-1-benzopyran-6-yl hydrogen phosphate] potassium salt on lipid peroxidation and phospholipase activity.'**
- **NIPPON GEKA GAKKAI ZASSHI vol. 93, no. 8 , 1992 pages 833 - 841 M. OBATA 'Investigation of lipidperoxidation in regenerating rat liver.'**

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Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a useful lipid metabolism improving medicinal composition. More particularly, this invention relates to a useful lipid metabolism improving medicinal composition containing an ascorbyl tocopheryl phosphate compound or a pharmacologically acceptable salt thereof.

2. Description of the Prior Art

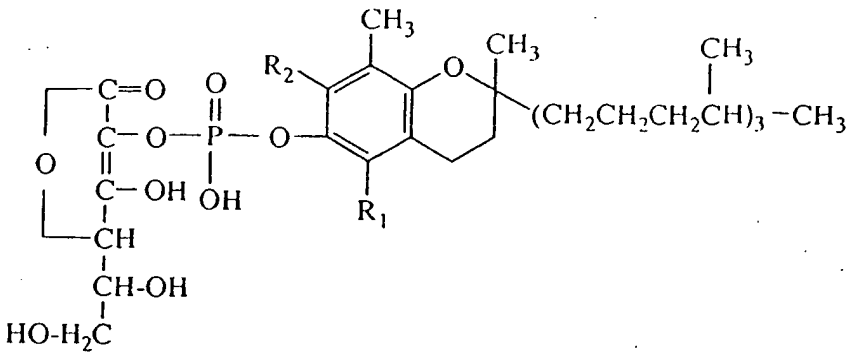
Hyperlipidemia is generally considered to be a risk factor for arteriosclerosis. It is also known that arteriosclerotic changes occur as plasma lipids, particularly cholesterol, adhere to, and become deposited on, the arterial wall. Recent advances in research in this field have shown that an increase in low-density lipoprotein (LDL), among plasma lipids, plays a major role in the pathogenesis of arteriosclerosis, while high-density lipoprotein (HDL) contributes to the removal and decomposition of the cholesterol which has been deposited on the vascular wall and cell membrane, thus acting as an antiarteriosclerotic factor.

Therefore, with the view of treating and preventing hyperlipidemia, which may be of divergent etiologies, and of arteriosclerosis and other diseases associated with hyperlipidemia, efforts are being made to develop blood cholesterol-lowering drugs, particularly drugs which would reduce the low-density lipoprotein level and increase the high-density lipoprotein level in the blood.

Under the circumstances, the inventors of this invention explored for compounds having potent lipid metabolism-improving activity. As a consequence, the inventors discovered that certain ascorbyl tocopheryl diester compounds of phosphoric acid and their pharmacologically acceptable salts have meritorious lipid metabolism-improving activity, for example the action to reduce LDL and increase HDL effectively and, based on this finding, did further research to complete this invention.

SUMMARY OF THE INVENTION

This invention relates to a the use of lipid metabolism improving medicinal composition containing a phosphoric acid diester compound of the following formula (hereinafter referred to as the present compound) or a pharmacologically acceptable salt thereof.



(wherein R_1 and R_2 are the same or different and each represents a hydrogen atom or a methyl group).

DETAILED DESCRIPTION OF THE INVENTION

The present compound to be used in the lipid metabolism improving medicinal composition of this invention can be synthesized by the processes described in, inter alia, Japanese Patent (JP) Publication Hei-2-44478 and JP Hei-5-23274 or any processes analogous thereto.

The present compound for use in the lipid metabolism improving composition of this invention is already known to be of value as an anticataract drug, a prophylactic and therapeutic drug for climacteric disturbance, a skin-beautifying cosmetic (JP Publication Hei-2-44478), an anti-inflammatory drug (JP Publication Hei-1-27044), an antiulcer drug (JP Kokai S-63-27062) and a prophylactic and therapeutic agent for ischemic disorder in organs (JP Kokai Hei-2-111722),

for instance.

The present compound, as a lipid metabolism improving agent, can be employed for purposes of this invention regardless of whether it is the free acid form or a pharmacologically acceptable salt thereof. The salt may be an alkali metal salt such as the sodium salt and the potassium salt, or an alkaline earth metal salt such as the calcium salt and the magnesium salt. Any other salts, if pharmacologically acceptable, can also be employed.

The lipid metabolism improving medicinal composition of this invention may contain any one or, if necessary, more than one species of the present compound depending on the intended use and need.

The present compound as the active ingredient of the lipid metabolism improving medicinal composition of this invention is sparingly toxic and, therefore, safe clinically, wherefore it can be put to use with advantage [LD_{50} of the monopotassium salt of phosphoric acid diester of L-ascorbic acid, DL-α-tocopherol (hereinafter referred to briefly as EPC-K_1) is ≧ 5 g/kg p. o. (rats), ≧ 100 mg/kg i.v. (rats)].

The lipid metabolism improving medicinal composition of this invention can be administered orally or parenterally for the treatment or prevention of hyperlipidemia due to various causes and of arteriosclerosis and other diseases associated with hyperlipidemia. It can be used in various dosage forms, e.g. solid preparations such as tablets, granules, powders, capsules, etc. and liquid preparations such as injections, all of which can be manufactured by the established pharmaceutical procedures. These dosage forms may contain a variety of additives which are commonly employed, such as excipients, reabsorption promoters, buffers, surfactants, solubilizer, preservatives, emulsifiers, isotonizing agents, stabilizers, pH control agents, etc., each in a suitable amount or proportion.

The dosage of the present compound for use as a lipid metabolism improving agent is dependent on species of the present compound, type of diseases, patient's age, and body weight, therapeutic regimen, etc. but taking an injection as an example, about 1 mg to about 100 mg per adult man can be administered once a day and in the case of an oral preparation, about 10 mg to about 1,000 mg can be administered a few times a day.

The lipid metabolism improving medicinal composition of this invention may further contain, unless contrary to the object of the invention, one or more other lipid metabolism improving agents and/or other pharmacologically active ingredients.

EXAMPLES

The following experimental and working examples are further illustrative of this invention.

[Test Example 1] Effect of the present compound on high cholesterol diet-fed hyperlipidemic rats

The effect of the present compound administered orally was evaluated in high cholesterol nicotinate, both of which are commercially available, as reference drugs.

[Test substances]

(1) L-Ascorbyl DL-α-tocopheryl phosphate monopotassium (EPC-K_1) 100 mg/kg and 200 mg/kg p.o. (dissolved in distilled water)
(2) Probucol 200 mg/kg p.o. (suspended in 0.5% CMC)
(3) Tocopherol nicotinate 200 mg/kg p.o. (suspended in 0.5% CMC)

[Methods]

Male SD rats purchased from Clea Japan were used (4 weeks of age). These animals were fed on a cholesterol (1%)-containing solid food (Nihon Nosan Kogyo K.K.) to construct rat models of hyperlipidemia. The test substance was administered once a day for 12 days. On the 12th day, blood samples were collected for the determination of total lipid (TL), phospholipids (PL), triglycerides (TG), total cholesterol (T-ch), free cholesterol (F-ch), esterified cholesterol (E-ch), non-esterified fatty acids (NEFA), lipid peroxides (LPO), HDL-cholesterol (HDL-ch), β-lipoprotein (β-LP) and lipoprotein fractions. Normal solid food (Nihon Nosan Kogyo K.K.) was supplied to rats in the normal group.

[Results]

The results are shown in Table 1. It is apparent from Table 1 that the present compound at 200 mg/kg significantly lowered total cholesterol (T-ch), free cholesterol (F-ch), esterified cholesterol (E-ch) and lipid peroxide levels. Moreover, the present compound lowered total cholesterol (T-ch), free cholesterol (F-ch), esterified cholesterol (E-ch) and total lipid (TL) by the same degrees as did 200 mg/kg of probucol and 200 mg/kg of tocopherol nicotinate.

[Table 1]

Group Dose (mg/kg)	Control group	EPC-K_1 100	EPC-K_1 200	Probucol 200	Tocopherol nicotinate 200	Normal group
Triglycerides	45 ± 17	50 ± 20	49 ± 14	43 ± 14	39 ± 17	82 ± 24
Total cholesterol	307 ± 89	257 ± 72	239 ± 59 *1	240 ± 40 *1	247 ± 50	75 ± 10
Free cholesterol	54 ± 18	44 ± 13	40 ± 13 *1	38 ± 8 *2	42 ± 10 *1	12 ± 2
Esterified cholesterol	251 ± 73	213 ± 60	198 ± 47 *1	202 ± 32 *1	205 ± 41	63 ± 8
HDL-ch	28 ± 7	29 ± 7	29 ± 4	29 ± 5	32 ± 6	45 ± 4
β-Lipoprotein	726 ± 184	633 ± 157	608 ± 145	598 ± 101	602 ± 109	190 ± 37
LDL	227 ± 131	238 ± 67	256 ± 94	274 ± 99	304 ± 61	169 ± 40
VLDL	597 ± 326	491 ± 268	416 ± 237	381 ± 154 *1	368 ± 174 *1	5 ± 3
Free fatty acids	1116 ± 331	1115 ± 312	1139 ± 353	1249 ± 284	1041 ± 150	725 ± 192
Phospholipids	180 ± 29	174 ± 19	172 ± 17	168 ± 15	171 ± 15	145 ± 11
Total lipid	668 ± 146	610 ± 115	580 ± 104	570 ± 76 *1	582 ± 80	340 ± 36
Lipid peroxides	18 ± 5	17 ± 4	14 ± 4 *1	17 ± 3	14 ± 4 *1	26 ± 5

Each value represents the mean± S.D.
Significant difference of the test substance compared to the control group *1: $p<0.05$, *2: $p<0.01$, n=8-17.

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[Test Example 2] Effect of the present compound on streptozotocin-induced hyperlipidemia in rats

The effect of the present compound administered orally was compared with that of probucol in rats with streptozotocin-induced hyperlipidemia.

[Test substances]

EPC-K_1 125 and 250 mg/kg (dissolved in distilled water)
Probucol 125 mg/kg (suspended in 0.5% CMC)

[Method]

Streptozotocin 50 mg/kg was injected into the tail vein of Wistar rats (4-week-old) to induce hyperglycemia and hyperlipidemia. Blood samples for biochemical tests were collected 24 hours after administration of streptozotocin. The test substance was administered orally 1 hour before administration of streptozotocin.

[Results] The results are shown in Table 2. As apparent from Table 2, the present compound at 125 and 250 mg/kg caused significant decreases in triglycerides (TG), lipid peroxides (LPO), non-esterified fatty acids (NEFA) and total lipid (TL). Referring to cholesterol fractions, the present compound caused an overt increase in high-density lipoprotein (HDL) and overt decreases in low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). Probucol 125 mg/kg lowered triglycerides (TG), non-esterified free acids (NEFA) and total lipid (TL) by substantially the same degrees as the present compound did rather elevated the very-low-density lipoprotein (VLDL) level and failed to lower lipid peroxides (LPO).

[Table 2]

Group Dose (mg/kg)	Control group	EPC-K_1		Probucol	Normal group
		125	250	125	
Triglycerides	292 ± 95	195 ± 75*1	192 ± 76*1	191 ± 81	153 ± 23
Total cholesterol	63 ± 7	60 ± 5	64 ± 7	55 ± 5	61 ± 5
Free cholesterol	14 ± 6	10 ± 2	12 ± 3	10 ± 2	12 ± 2
Esterified cholesterol	50 ± 6	50 ± 5	51 ± 8	45 ± 5	49 ± 3
HDL (%)	89.0 ± 4.8	95.0 ± 2.8	95.6 ± 0.7	86.2 ± 3.9	88.9 ± 4.4
VLDL (%)	5.5 ± 1.7	2.8 ± 1.8	2.5 ± 0.6*1	9.2 ± 2.2*1	7.0 ± 2.8
LDL (%)	5.5 ± 3.8	2.2 ± 1.2	1.9 ± 0.4	4.7 ± 2.0	4.1 ± 2.0
HDL/LDL ratio	253 ± 222	638 ± 438	524 ± 144	221 ± 104	290 ± 190
β-Lipoprotein	492 ± 168	327 ± 128	329 ± 133	327 ± 143	247 ± 37
Lipid peroxides	30.4 ± 1.6	29.4 ± 1.6*1	24.4 ± 3.6*1	30.0 ± 1.2	29.4 ± 2.3
Free fatty acids	3538 ± 1049	2370 ± 611*2	2542 ± 785*1	2794 ± 1015	915 ± 126
Phospholipids	164 ± 15	152 ± 15	155 ± 15	140 ± 14*1	147 ± 10
Total lipid	553 ± 115	437 ± 93*1	443 ± 92*1	414 ± 94	392 ± 35
Blood glucose	599 ± 43	586 ± 46	585 ± 34	629 ± 17	171 ± 13

Each value represents the mean± S.D. n=8-7 Significant difference of the test substance compared to the control group *1: $p<0.05$, *2: $p<0.01$.

[Test Example 3] Effect of the present compound on Triton WR-1339-induced hyperlipidemia in rats

The effect of the present compound given orally was evaluated in rats with Triton WR-1339-induced hyperlipidemia.

[Test substances]

EPC-K_1 250 mg/kg (dissolved in distilled water)
Probucol 250 mg/kg (suspended in 0.5% CMC)

[Methods]

Triton WR-1339 (Nakalai Tesque) 100 mg/kg was injected into the tail vein of Wistar rats (6 weeks of age) to construct rat models of hyperlipidemia. Each test substance was administered orally 1 hour before administration of Triton WR-1339. Blood samples for biochemistry tests were collected 24 hours after administration of Triton WR-1339.

[Results]

The results are shown in Table 3. As seen from Table 3, the present compound at 250 mg/kg significantly lowered triglycerides (TG) and nonesterified fatty acid (NEFA) levels. On the other hand, probucol failed to produce falls in these parameters.

Table 3

Group Treatment group (mg/kg)	Control group	EPC-K1 250	probucol 250
Triglycerides	182± 36	120± 34 *1	164± 32
Total cholesterol	72± 14	83± 7	71± 7
HDL-ch	49± 15	56± 8	49± 6
β-Lipoprotein	213± 78	147± 66	190± 52
LDL	221± 34	183± 43	200± 37
VLDL	60± 42	33± 19	40± 28
Free fatty acids	709± 92	554± 96 *1	643± 41
Phospholipids	136± 18	130± 13	130± 14
Total lipid	426± 29	374± 41	400± 50
Lipid peroxides	24± 3	18± 5	27± 2
Each value represents the mean± S.D. n=6. Significant difference of the test substance compared to the control group: *1, $p<0.05$.			

[Example 1] Oral tablet

EPC-K_1	100mg
Lactose	75mg
Starch	20mg
Polyethylene glycol 6000	5mg

The above ingredients are mixed in the conventional manner to provide a tablet. Where necessary, the tablet may be sugar-coated.

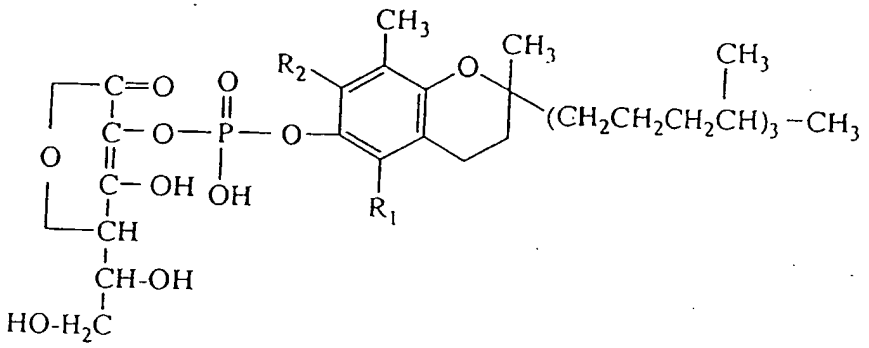
[Example 2] injection

EPC-K_1	200mg
Mannitol	5.0 g
Sodium hydroxide, 1N soln.	q.s.
Distilled water	To make 100 ml
pH=6.5	

The above ingredients are mixed and filtered through a bacterial filter. The filtrate is aseptically distributed into glass ampule, 5 ml per ampule, followed by sealing by fusion of the glass to provide an injection.

Claims

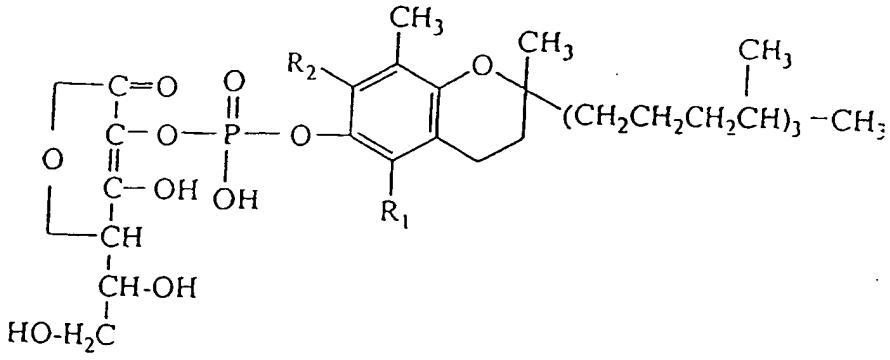
1. Use of a phosphoric acid diester compound of the formula or a pharmacologically acceptable salt thereof,



wherein R_1 and R_2 are the same or different and each represents a hydrogen atom or a methyl group, for the preparation of a Lipid metabolism improving medicinal composition.

Patentansprüche

1. Verwendung einer Phosphorsäurediesterverbindung der Formel

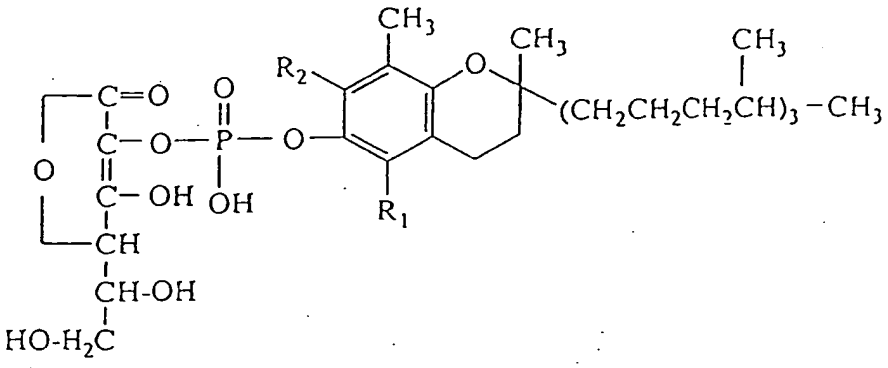


wobei R_1 und R_2 gleich oder verschieden sind und jeweils ein Wasserstoffatom oder eine Methylgruppe darstellen,

oder eines pharmakologisch annehmbaren Salzes davon, zur Herstellung einer medizinischen Zusammensetzung zur Verbesserung des Lipidstoffwechsels.

Revendications

1. Utilisation d'un composé diester d'acide phosphorique ayant la formule suivante, ou d'un de ses sels acceptables en pharmacie :



dans laquelle R_1 et R_2 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe méthyle, pour la préparation d'une composition médicale améliorant le métabolisme des lipides.